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R72P Polymorphism of TP53 in Ulcerative Colitis Patients is Associated with the Incidence of Colectomy, Use of Steroids and the Presence of a Positive Family History

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Abstract P53 tumor suppressor protein is one of the pivotal regulators for genome integrity, cell cycle and apoptosis. The most commonly and extensively studied single nucleotide polymorphism (SNP) of p53 is Arg>Pro substitution on codon 72 (R72P). Although we know that the SNP has unique functional effects on the protein, its clinical significance is not clearly identified yet. Aim of the study was to access the relationship between R72P genotype distribution and clinical variables in patients with ulcerative colitis (UC) and colorectal cancer (CRC). Genomic DNA samples were extracted from 95 UC, 50 CRC, and 219 healthy controls. R72P genotype analysis was carried out with polymerase chain reaction following by restriction enzyme digestion. We observed that Pro allele carriage is a strong risk factor for CRC (OR=3.03; 95%CI=1.91–2.40; p=0.003), but only modest association with UC (OR=1.61; 95%CI=0.98–2.65; p=0.059) (Pro/Pro and Pro/Arg genotypes vs. Arg/Arg genotype). We did not find any correlation between genotype distribution of the polymorphism and clinical parameters of CRC, but in UC, Pro/Pro genotype was significantly related to an inflammatory bowel disease family history (OR=8.0; 95%CI=1.68–38.08, p=0.015), and Arg/Pro genotype was significantly associated with the history of disease-related colectomy (OR=17.77; 95%CI=0.98–323.34, p=0.012) and steroid use (OR=10.14; 95%CI=2.63–39.12, p=0.0002). Our data suggest that R72P variant seems to be associated with high risk for development of CRC but carries low risk for development of UC. R72P genotypes might be a useful predictive marker for surgical and medical treatment of UC.

Keywords p53 · Codon 72 polymorphism · Colorectal cancer · Ulcerative colitis · Colectomy · Steroid · Family history

Introduction

Apart from point mutations, polymorphic variants in the TP53 (*geneID: 7157*) locus might determine its function and cancer-related phenotypical effects. The polymorphism at codon 72 encodes either an arginine amino acid (Arg/72R) or a proline residue (Pro/72P) and localizes on exon 4 in the polyproline domain. Mutation of the domain is not a common location in tumor, but this domain is essential for apoptotic response and inhibition of tumorogenesis [1, 2]. Functional analysis studies show that R72P polymorphism changes p53 protein properties by different ways and plays a pivotal role in cancer development [3]. The polymorphism has potential modifier capacity of mutant p53 protein [4], and also determines transcript levels of p53 [5]. Arginin allele of codon 72 has been found to be a more potent inducer of apoptosis than proline allele [6]. Clinically, R72P polymorphism might affect prognosis and response to

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treatment in different types of cancer [7–9]. However, a consensus is not reached yet on the identification of the alleles or variants that would provide more benefit for clinical applications in patients with cancer or cancer-related diseases.

Ulcerative colitis (UC) is one of the chronic inflammatory bowel diseases with an increased risk for the development of colorectal cancer (CRC) [10]. Although we know that p53 alterations in UC may affect the development of CRC [11–13], and dysplasia [14, 15], there is no sufficient data to verify the clinical significance of the well-known polymorphism of the tumor suppressor protein in patients with UC. In this study, we investigated R72P variant of p53 in colorectal cancer and ulcerative colitis patients, and the possible correlations with the clinical variables and phenotypes of these patients.

Table 1 Demographic and clinical features of the UC patients

Characteristics	Ulcerative colitis
Male *n (%)*	46 (48)
Female *n (%)*	49 (52)
Age: mean±SD (min to max)	44.8±16.3 (17 to 91)
Age at onset: mean±SD (min to max)	32.2±13 (9 to 61)
Duration of disease: mean±SD (min to max)	1.95±3.86 (1 to 20)
IBD family history *n (%)**	12 (12.6)
Smoking *n (%)*[a]	28 (29.2)
Localization of the disease	
Proctitis *n (%)*	12 (12.6)
Distal colonic *n (%)*	44 (46.3)
Pancolitis *n (%)*	39 (41.1)

[a] Number is available only in 75 and 83 patients with UC for IBD family history and smoking, respectively

Material & Methods

Study Population

CRC Cases Tissue samples from 50 CRCs were obtained with consent from patients who underwent curative surgical resection from 1990 to 2003 at the Marmara University Hospital Department of General Surgery. The patient group included 28 women and 22 men with ages ranging from 38 to 86 (median 62 years). Totally, 36 tumors were localized in the colon and 14 were in the rectum. All the tumors were diagnosed as adenocarcinomas and according to the TNM system of UICC (International Union against Cancer) they were staged as stage I or II. The distribution of cases using WHO grading system was as follows: 11 low, 28 moderate, and 11 high-grade adenocarcinomas.

UC Cases Ninety five patients with UC were recruited from the Gastroenterology Clinic of Marmara University School of Medicine and the Marmara University Gastroenterology Institute between 1998 and 2005. The diagnosis of UC was established by endoscopic, radiological, pathological and clinical criteria [16]. Demographic and clinical data including sex, age of onset, duration of disease, location of disease, family history [presence of inflammatory bowel disease (IBD) in 1st and 2nd degree relatives], and smoking behavior were obtained through patient interviews and medical chart reviews retrospectively (Table 1). Drugs used including steroids and immunomodulators were noted and steroid dependency was determined as patient's response to steroid therapy but inability to tapering the drug doses [17]. Colectomy was applied if medical treatments were unsuccessful or if complications have developed.

Controls The control group consisted of 219 healthy volunteers with similar race from the same geographical region and were matched for age and gender. People who have had family history for any type of tumor or chronic inflammation bowel diseases were not included in the study. The study protocol was approved by the local Ethics Committee of the Marmara University School of Medicine.

DNA Extraction

DNA isolation was carried out from paraffin blocks for CRC. Archival materials were evaluated to select a representative tumor block for each case by an experienced pathologist. Genomic DNA was extracted from the tissue specimens using a standard phenol/chloroform and proteinase K method described previously [18]. Two ml of venous blood from UC and healthy subjects were collected in tubes containing EDTA and then stored at +4°C. Genomic DNA was isolated from peripheral blood leukocytes using the phenol/chloroform method within 1 week.

Analysis of Codon 72 (Arg>Pro) Polymorphism

Region of R72P variants in the exon 4 were detected by PCR amplification following by digestion with Bsh1236I (BstU I) enzyme [19]. A 199-bp fragment of P53 gene was amplified using forward primer: 5′-TTGCCGTCCCAAGCAATG GATGA-3′ and Reverse primer: 5′-TCTGGGAAGGGACA GAAGATGAC-3′. The PCR amplification was performed in a final volume of 50 µl containing 100 ng genomic DNA, 3 mM $MgCl_2$ (MBI Fermentas, Lithuania) 0.4 mM each dNTP mix (MBI Fermentas, Lithuania), 0.2 µM each of primer, 1.5U Taq polymerase (MBI Fermentas, Lithuania) its 1× buffer. PCR began with 94°C for 2 min, followed by 35 cycles of 94°C for 30 s, 60°C for 30 s and 72°C for 30 s with the final extension step at 72°C for 7 min. The

Table 2 Allele frequencies of R72P SNP in patients with CRC and UC

	Arg n (%)	Pro n (%)	Total	*p*
CRC	52 (52)	48 (48)	100 (100)	0.0032
UC	117 (62)	73 (38)	190 (100)	0.145
Control	296 (68)	142 (32)	438 (100)	

P values obtained by *chi*-square test for comparing CRC and UC versus control group

amplified PCR products were digested overnight at 37°C in a 30 µl reaction volume containing ten units of Bsh1236I (MBI Fermentas) and 1× reaction buffer. The restriction products were loaded on ethidium bromide-stained % four nusieve agarose gel (% three nusieve+%1 agarose) and then visualized under UV light. The *Arg/Arg* homozygote was cleaved by Bsh1236I to yield 113 and 86-bp bands. The *Pro/Pro* homozygote was not cleaved by Bsh1236I and yielded a single 199-bp band. The *Arg/Pro* heterozygote contained all three bands (199 bp,113 bp, 86 bp) following restriction digestion.

Statistical Analyses

All statistical analyses were performed on grouped patients as CRC, UC, and controls. Continuous variables, expressed as mean±SD, were compared by parametric or nonparametric ANOVA and t tests as appropriate. The comparison of the distribution of the R72P variants in demographic and phenotypic characteristics of CRC and UC were calculated by χ^2 statistics or two-tailed Fisher's exact test. The test was also applied for identifying the deviations from the Hardy-Weinberg proportion. Odds ratios (ORs) as estimates of relative risk of the disease were calculated based on 95% confidence intervals (CI). InStat statistical program was used. A "p" value less than 0.05 was considered statistically significant.

Results

The p53 R72P genotype distribution in the CRC, UC and control groups were in Hardy-Weinberg equilibrium ($p>0.05$). Allele frequencies of R72P variants of p53 are shown in Table 2. When we analyzed allele frequencies of the polymorphism in both of the diseases, we observed that Pro allele was at a 1.92-fold (95% CI=1.91–2.40; $p=0.003$) increased risk of CRC compared with the respective control group. There were no statistically significant correlations in UC compared with the control group concerning about the allele frequencies.

The p53 R72P genotype distributions in the CRC and UC groups are summarized in Table 3. Frequencies of Pro allele carriers (Arg/Pro and Pro/Pro genotypes) were significantly higher in the CRC group than the controls (OR 3.03; 95%CI=1.48–6.23, $p=0.001$). On the other hand, we detected Pro allele carriage in only borderline significance (OR 1.61; 95%CI=0.98–2.65; $p=0.059$) in UC cases. The genotype frequencies of Pro allele carriage were 78%, 67% and 54% and the frequencies of Arg/Arg genotype were 22%, 33% and 46% in CRC patients, UC patients and control group, respectively. Our results from the CRC patients showed that Pro allele carriage was associated with an increased risk of colorectal cancer, but the allele had a modest significance related with the prediction of UC.

We examined the relationship between clinical parameters and the genotypes of R72P SNP in both of the diseases. In the CRC patients group, the polymorphism was not related with age, sex, tumor localization, grade, stage or relapse. On the other hand, when the genotype effects of the SNP were studied in relation to the clinical variables of the UC, positive correlations were found with the family history, steroid use and colectomy risk in the UC patients group. Table 4 shows the R72P genotypes and their association with clinical parameters in the UC group. Pro/Pro genotype was significantly associated with an IBD family history in the UC cases (OR 8.0; 95%CI=1.68–38.08, $p=0.015$). Four of the nine patients with IBD family history had Pro/Pro genotype. On the other hand, Arg/Pro genotype was significantly associated with the presence of colectomy history (OR 17.77; 95%CI=0.98–323.34, $p=0.012$) and the use of steroids (OR 10.14; 95%CI=2.63–39.12, $p=0.0002$) in the UC group. All of the patients with a positive colectomy history ($n=7$) and 17 of 20 patients with a positive history for steroid use had Arg/Pro

Table 3 Genotype distributions of R72P polymorphism in patients with CRC and UC

	Arg/Arg n (%)	Arg/Pro n (%)	Pro/Pro n (%)	Total n (%)	*p*
CRC	11 (22)	30 (60)	9 (18)	50 (100)	0.001
UC	33 (35)	51 (55)	11 (12)	95 (100)	0.059
Control	101 (46)	94 (43)	24 (11)	219 (100)	

P values obtained by *chi*-square test for comparison between Pro allele carriers (Arg/Pro and Pro/Pro genotypes) and Arg/Arg genotypes

Table 4 R72P genotypes and association with clinical parameters in patients with UC

Clinical variables	*R72P Genotype*		
	Arg/Arg	Arg/Pro	Pro/Pro
Sex			
Male (44)	18 (40.9)	22 (50)	4 (9.1)
Female (51)	15 (29.4)	29 (56.9)	7 (13.7)
Localization			
Proctitis (8)	2 (25)	4 (50)	2 (25)
Distal (38)	17 (44.7)	16 (42.1)	5 (13.2)
Pancolitis (30)	10 (33.3)	18 (60)	2 (6.7)
IBD family history*			
Negative (66)	25 (37.9)	35 (53)	6 (9.1)
Positive (9)	4 (44.4)	1 (11.1)	4 (44.4)
Colectomy history*			
Negative (70)	29 (41.4)	32 (45.7)	9 (12.9)
Positive (7)	0 (0)	7 (100)	0 (0)
Use of steroids*			
Negative (53)	26 (49.1)	19 (35.8)	8 (15.1)
Positive (20)	2 (10)	17 (85)	1 (5)
Use of immuran			
Negative (73)	29 (39.7)	35 (47.9)	9 (12.4)
Positive (11)	1 (9.1)	9 (81.8)	1 (9.1)
Smoking			
Negative (56)	19 (33.9)	30 (53.6)	7 (12.5)
Positive (27)	11 (40.7)	13 (48.1)	3 (11.2)

*$P<0.05$

genotype. Table 5 represents the relationship between R72P genotype and the associated clinical findings.

Discussion

Mutations and polymorphisms in p53 gene are associated with different types of tumors and related diseases, but little is known about the relationship between common p53 polymorphisms and their clinical value in UC and CRC. One of the p53 genetic polymorphisms, R72P is a unique modifier of apoptotic potential of the protein. Therefore, we aimed to find out the relationship between the most common R72P SNP of p53 and clinical variables in our UC and CRC patients. We found that risk of CRC was associated with Pro allele carriage that was 3-fold greater in patients than in healthy controls. On the other hand, presence of the allele had a modest significance for the prediction of UC compared with the controls.

P53 R72P SNP had been studied in different populations, but a consensus about which allele carries potential high risk for development of CRC has not been reached yet. To the best of our knowledge there has been only one study in the literature from Turkish population concerning about R72P variant of p53 in colon cancer [20]. In this study, any significant difference in colon cancer patients in relation to R72P variant carriage of p53 was not observed (n=67). However, in the current study the population groups were collected from the same region of the country, and the patients consisted of both colon and rectum cancer patients that were pooled together. Moreover, our control group (n=219) was greater with respect to the control group in the study conducted by Sayhan et al. (n=76) [20]. Due to these differences, in our study, we found that R72P polymorphism was significantly higher in the CRC patients than the healthy controls in the studied Turkish population.

In Chinese [21] and Korean [22] populations, Pro/Pro genotype was associated with an increased CRC risk (OR= 2.37 and 1.88, respectively), and a weak association was shown in Spain population [5]. Inversely, other studies from Argentina and Greece found that Arg/Arg genotype had a 2.08-fold and 2.98-fold increased risk of CRC development, respectively [23, 24]. The data of Swedish [25] and the United States [26] studies did not show a significant relationship between p53 codon 72 SNP and CRC risk. In a study in Swedish population, 91 patients and 206 controls were studied and any allelic or genotypic differences

Table 5 Relationship between R72P genotype and IBD family history, the presence of colectomy and the use of steroids in UC cases

Clinic parameter	Genotype	Negative n (%)	Positive n (%)	OR (95% CI)	*p*
Family history (n=75)	Pro/Pro	6 (9.1)	4 (44.4)	8.00 (1.68–38.08)	0.015
	Others*	60 (90.9)	5 (55.6)	1 (reference)	
Colectomy (n=77)	Arg/Pro	32 (45.7)	7 (100)	17.77 (0.98–323.34)	0.012
	Others**	38 (54.3)	0 (0)	1 (reference)	
Use of steroids (n=73)	Arg/Pro	19 (35.8)	17 (85)	10.14 (2.63–39.12)	0.0002
	Others**	34 (64.2)	3 (15)	1 (reference)	

OR odds ratio

[a] Arg/Arg and Arg/Pro genotype

[b] Arg/Arg and Pro/Pro genotypes

between the UC and control groups considering codon 72 polymorphism was not found, but a statistically significant difference (p=0.036) in distribution of codon 72-MspI haplotypes was shown [25]. Also, in a study in Italian population, any difference between the UC cases and controls regarding the allelic frequencies and the distribution of genotypes on R72P polymorphism was not observed [27]. These findings were consistent with our data about the allele frequencies of codon 72 SNP. However, in our study a minor difference on genotype distribution has been observed that was found to be close to statistical significance (p=0.059), suggesting that Pro allele carriage in our population may be a mild modifier of other risk factors in the development of UC.

In a study in Italian population [27], a relationship between clinical course, duration of disease, maximal extension, CRC family history and p53 R72P genotype was observed. However, we could not evaluate the clinical course and CRC family history due to the insufficient clinical records and to the fact that most of our patients had a short duration of UC disease (≤7 years). On the other hand, we detected that Pro/Pro genotype had an 8-fold increased rate of prevalence in patients with IBD family history.

To the best of our knowledge, our study has been the first to show that p53 R72P polymorphism could be a reliable parameter of the refractory or extensive disease. We found that p53 R72P polymorphism was correlated with disease-related colectomy history and steroid resistance. Approximately 15–20% of the patients with UC have severe symptoms and remain refractory to the most of the medical therapies [28, 29]. In about 35–40% of UC patients, who do not respond to medical therapy such as steroid therapy or who develop severe hemorrhage or perforation, surgical treatment (colectomy) becomes necessary [28]. In this regard, our data provided useful information on the potential clinical use of Arg/Pro genotype as a good predictive marker for colectomy risk and steroid resistance.

Chronic inflammation and apoptosis of inflammatory cellular components are key mechanisms involved in pathogenesis of UC and also in determining disease severity [30–33]. Previous experimental studies demonstrated that p53 with the Pro allele induces apoptosis less effectively than p53 with the Arg allele [34, 35]. Therefore, p53 Pro allele may cause a poor response to steroid, the therapeutic activity of which involves the reduction of anti-apoptotic activity [32]. Moreover, it is reported that p53 is a general inhibitor of inflammation that acts as an antagonist of NF-κB in vivo [36]. Some of the inflammatory mediators have a role the etiology of UC and they can be differently regulated by polymorphic allele of p53 gene. Thus, it can be speculated whether this regulation is due to change in transcriptional activity of p53 variants or its protein interaction capacity. Another possibility is that this genetic variation may only be a genetic marker rather than an etiological factor for disease severity of UC.

In conclusion, our study provided evidence that R72P polymorphism of p53 gene has been strongly associated with the CRC development in the Turkish population, while a weaker relationship was found with the development of UC. Pro/Pro genotype might be a useful marker to predict the presence of IBD in the relatives of the patients. Arg/Pro genotype might be a good predictive marker to distinguish the high-risk patients for early surgical option and the rest can be followed up with routine medical therapy. Further studies are needed to clarify the clinical significance of the polymorphisms in the prediction of high-risk patients in IBD groups.

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